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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/762,587 | 09/06/2001 | Antonio Grillo-Lopez | PM0277847 | 5272 |

47553 7590 04/04/2005

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| EXAMINER | |
|---|---|
| DAVIS, MINH TAM B | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1642 | |

DATE MAILED: 04/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/762,587 | GRILLO-LOPEZ, ANTONIO | |
| | Examiner | Art Unit | |
| | MINH-TAM DAVIS | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *09 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) 7 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 7 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant asserts that the Office action refers to claim 1. Applicant asserts that however, the sole claim pending after entry of the Examiner's amendment entered in the Notice of Allowability mailed on 10 March 2004 is claim 7, and that the renumbering of the claim for issue does not have effect in view of the Request for Continued Examination (RCE) in this application.

The Examiner agrees that the claim number should be claim 7 and not claim 1. The Examiner apologizes for any inconvenience incurred.

Accordingly, claim 7 is examined in the instant application.

The following are the remaining rejections.

## OBJECTION

Claim 7 is objected to, because the amended format of claim 7 is not correct. That is the "anti-CD20" language previously recited in claim 7 in the Examiner amendment of 03/10/04 and in Applicant's amendment of 02/19/04 is missing in the claim.

## REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE, NEW REJECTION

Claim 7 is rejected under 35 USC, 112 first paragraph, because while being enabled for a method for treating a subject having CD20-positive B cell

lymphoma, wherein said subject is refractory to treatment with a non-radiolabeled rituximab antibody, comprising administering an iodine-131-labeled anti-CD20 antibody, **the specification is not reasonably enabled for a method for treating a subject having CD20-positive B cell lymphoma, wherein said subject is refractory to treatment with a non-radiolabeled rituximab antibody, comprising administering "an iodine-131-labeled murine antibody".** The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 7 is drawn to a method for treating a subject having CD20-positive B cell lymphoma, wherein said subject is refractory to treatment with a non-radiolabeled rituximab antibody, comprising administering an iodine-131-labeled murine antibody.

Claim 7 encompasses a method for treating a subject having CD20-positive B cell lymphoma, wherein said subject is refractory to treatment with a non-radiolabeled rituximab antibody, comprising administering **any iodine-131-labeled murine antibody,** wherein said antibody is not necessarily specific for and target CD20 positive B-cell lymphoma.

One cannot extrapolate the teaching in the specification to the claim. One cannot predict that administering any iodine-131-labeled murine antibody, wherein said antibody is not necessarily specific for and target CD20 positive B-cell lymphoma, would be useful for treating CD20 positive B-cell lymphoma, because said antibody would not be expected to bind to and kill specifically CD20 positive B-cell lymphoma. For example, said antibody could bind to and kill mainly normal cells.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

**REJECTION UNDER 35 USC 103**

Claim 7 remains rejected under 35 USC 103, as being obvious over Maaloney et al, in view of Press et al, or Kaminsky et al, 1996, or Kaminsky et al of US 6,287,537, and further in view of Wahl et al, for reasons already of record in paper of 08/10/04.

Applicant asserts that the specification specifies that "refractory" patients include those who have not exhibited appreciable tumor remission or regression after administration of a chimeric anti-CD20 antibody, as constrast to patients who have relapsed.

For the purpose of compact prosecution, and in view of Applicant's response, claim 7 does not include treating patients having CD-20 positive B cell lymphoma, who have relapsed.

Applicant argues that none of the references describe or suggest treating a patient with an antibody specific for the same antigen as an antibody to which the patient has become refractory, and thus the reference fail to define the patient population required by the claim. Applicant argues that none of the references teaches or suggests that 131-I anti-B1 would be useful for treating patients who are refractory to any anti-CD20 antibody, let alone refractory to rituximab.

Applicant argues that the Examiner is extrapolating teachings from the Kaminsky '537 reference, that it does not support. Applicant argues that the passage cited by the

Examiner (lines 47-40 of column 21) does not support the conclusion that unlabeled anti-B1 antibody is necessarily without therapeutic effect in the treated patients. Applicant argues that Kaminsky et al do not rule out the therapeutic effect due to the unlabeled antibody.

Applicant argues that the Kaminsky '537 does not express or teach that 131-I-anti-B1 should be used for treating patients that are refractory to unlabeled anti-B1. Applicant argues that the evidence favors the conclusion that the patients described in Example 1 of Kaminsky '537 are not refractory to therapy with unlabeled anti-B1.

Applicant argues that Wahl et al do not describe or suggest the use of radioimmuntherapy after treatment with any unlabeled antibody, and they do not identify any patients that are refractory to unlabeled anti-B1.

Applicant's arguments in paper of 02/09/05 have been considered but are found not to be persuasive for the following reasons.

It is noted that Maloney et al teach treating patients with low-grade non-Hodgkin's lymphoma using unlabeled Rituximab, wherein the response rate to unlabeled Rituximab treatment is 46%. Although Maloney et al do not specifically teach that that there are 54% of patients treated with unlabeled Rituximab, it is clear that 54% of the patients are refractory to Rituximab, and thus it would have been obvious to treat those patients refractory Rituximab, using radiolabeled I-131-antiCD20 antibody, in view of the teaching of the secondary references.

Further, contrary to Applicant's arguments, the Examiner did not and does not cite Kaminsky et al, '537 to support the conclusion that the unlabeled anti-B1 antibody is necessarily without therapeutic effect in the treated patients.

Rather, the Examiner position has been and is that the teaching of '537 clearly indicates that although unlabeled anti-B1 does have therapeutic effect, as taught by Kaminsky et al, '537, however, in cases wherein the first administration of the unlabeled B1 antibody does not produce an antitumor response, i.e. refractory to the antitumor effect of the unlabeled B1 antibody, the antitumor response is due to a targeted radiation effect of the labeled B1 antibody, as taught by Kaminsky et al, '537.

It is noted that Kaminsky et al of US 6,287,537 teaches radioimmunotherapy (RIT) of patients having non-Hodgkin's lymphoma, by administering first unlabeled anti-B1 antibody (which is the same as anti-CD20 antibody or B1 antibody), followed by I-131 labeled anti-B1, wherein it is hypothesized that the unlabeled antibody may help the radiolabeled antibody to bypass an antigenic sink, and allows its better access to tumor sites (column 21, second paragraph).

In the beginning of the fourth paragraph of column 21 of US 6,287,537, US 6,287,537 teaches that the antibody moiety of the I-125 labeled B1 (which is equivalent to unlabeled B1 antibody) could have anti-tumor effect, as shown in vivo in a human B cell xenograft nude mouse, probably by inducing antibody-dependent cellular cytolysis, complement-dependent cytolysis and apoptosis (column 21, lines 31-41). US 6,287,537 goes on and teaches in said paragraph that, however, in cases that a large amount of high doses of unlabeled B1 antibody administered, and in those cases in which an

antitumor response appears to occur only after an radioimmunotherapy dose (RIT) (emphasis added) (column 21, lines 48-50), a targeted radiation effect is likely, especially since targeting of radioisotope is found to be so high in these cases, and could result in delivery to tumor up to 120 cGy per tracer doses (column 21, lines 50-54).

One would have interpreted the teaching of US 6,287,537, "in those cases in which an antitumor response appears to occur only after an radioimmunotherapy dose (RIT) (emphasis added) (column 21, lines 48-50), a targeted radiation effect is likely", as meaning that in cases wherein the first administration of the unlabeled B1 antibody does not produce an antitumor response, i.e. refractory to the antitumor effect of the unlabeled B1 antibody, the antitumor response is due to a targeted radiation effect of the labeled B1 antibody.

Thus the teaching of US 6,287,537 clearly indicates that although unlabeled anti-B1 does have therapeutic effect, for those cancer cases that do not response to the unlabeled B1 antibody, i.e. refractory to the treatment by the unlabeled B1 antibody, the radiolabeled B1 antibody would produce an antitumor effect.

In other words, in view of the teaching of Kaminisky '537, it would have been obvious to treat those patients that are refractory to the treatment by unlabeled rituximab, such as those 64% of patients that are refractory to unlabeled rituximab in the reference by Maloney et al, using radiolabeled anti-CD20 antibody taught by Press et al, Kaminsky et al, 1996, Kaminisky et al, '537 and Wahl et al, with a reasonably expectation of success, because of the following reasons:

1) Said radiolabeled antibody has been successfully used for treating patients with B-lymphoma, or non-Hodgkin's lymphoma, as taught by Press et al, Kaminsky et al, 1996, Kaminisky et al, '537 and Wahl et al, and is superior than unlabeled anti-CD20, in view that the overall survival rate is 93%, as taught by Press et al, versus 46% from treatment with unlabeled CD20 antibody, as taught by Maloney et al, and

2) The teaching of US 6,287,537 clearly indicates that although unlabeled anti-B1 does have therapeutic effect, for those cancer cases that do not response to the unlabeled B1 antibody, i.e. refractory to the treatment by the unlabeled B1 antibody, the radiolabeled B1 antibody would produce an antitumor effect.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

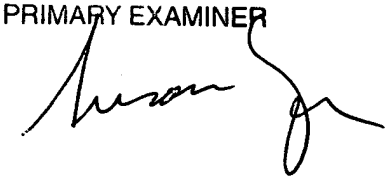
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SUSAN UNGAR, PH.D
PRIMARY EXAMINER



MINH TAM DAVIS

March 07, 2005